R E M A R K S

Responsive to the Office Action mailed on November 17, 2004, Applicants gratefully acknowledge the Examiner's indication that claims 1, 2, 6-8, 13, 14, 19, 25-27, and 29 are allowed. Claims 22, 23, and 28 are amended to more specifically claim the methods of treatment recited in those claims. No new matter is introduced by this Amendment. Claims 1, 2, 6-8, 10, 13-16, 19, 20, 22, 23, and 25-29 are pending in the application.

Election Of Species

The outstanding Office Action states that claims 10, 15, 16, 20, and 23 are withdrawn from consideration. In response to an election of species, Applicants had elected the species of invention that involves SEQ ID NO:30. Claims 1, 2, 6-8, 10, 13-16, 19, 20, 22, 23, and 25-29 all read on or relate to the elected species. Moreover, ***each of claims 10, 15, 16, 20, and 23 depends from allowed claim 1.*** Thus claim 1 is an allowable generic claim, so that each of the species included in claim 1 must likewise be allowable. As the Examiner will recall, when the elected species is found to be allowable, the Examiner must then examine other species that are embraced by a generic claim, which encompasses the allowable elected species. If no rejectable species is encompassed by that generic claim, all of the species and the generic claim, which encompasses them, must be allowed. Accordingly, an indication is respectfully solicited from the Examiner that claims 10, 15, 16, 20, and 23 are allowable along with claim 1.

Telephonic Interview

Examiner Mohamed contacted Applicants' representative Dr. Nuell telephonically on 10 November 2004 and indicated that certain amendments to claims 22, 23, and 28 would place this application into condition for allowance. The Examiner's rationale for rejecting claims 22 and 28 are reflected in the Office Action of November 17, 2004. Applicants are not able to agree to all of the changes to claims 22, 23, and 28 proposed by the Examiner in the telephonic interview. Applicants' position with respect to the rejection in question is set forth in this Amendment.

Background Of Invention

It is well known in modern medicine that tumors can be kept in a relatively harmless condition by anti-angiogenesis drugs. Cancers are life threatening when they are in late stages or have metastasized to other organs. Anti-angiogenesis drugs can prevent the tumor from further growth. In addition to the evidence already made of record in the present application concerning the state of the art with respect to general medical acceptance of anti-angiogenesis as a method for preventing tumor growth and metastasis, Applicants enclose herewith a copy of an article to this effect: Kate Ó Súilleabháin, "Despite Initial Setbacks, Researchers Are Focusing on Antiangiogenic Therapy More Than Ever", *OncoLog*, June 2004, Vol. 49, No. 6 (4 pages).

Written Description

Claims 22 and 28 were rejected under the first paragraph of 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. The Examiner alleges: "there is no description in the instant specification for the claimed methods of **preventing or treating a subject** ... by preventing or inhibiting tumor angiogenesis". Office Action, page 3, top (emphasis in original). The rejection is respectfully traversed. Reconsideration and withdrawal of this ground of rejection are earnestly solicited.

Typical of the claims in question is claim 23:

> 23. A method for preventing or treating primary ***tumor growth or metastasis*** by inhibiting tumor angiogenesis, said method comprising administering the composition of claim 15 to a subject presenting a tumor.

(Emphasis supplied.) The claims in question do not recite that tumors are being prevented (nor do they recite that a subject is being prevented). Instead, the claims recite (in part) that the ***growth or metastasis*** of tumors that already exist in a subject ("a subject presenting a tumor") is treated or prevented. Thus the invention in question involves (among other things) preventing tumor growth or metastasis.

The specification contains ample written description of this invention. For instance, "effective doses of the peptides of the present invention will be about 0.2 μg/kg/day to about 2 mg/kg/day for inhibition of ***metastasis***. ... the dosage ranges will be about 10-fold higher for inhibition of primary tumor ***growth***." Specification, page 8, lines 6-11.

The Examiner asserts: "Example 4 demonstrates that angio-3 can inhibit endothelial cell proliferation and retard tumor growth in mice. However, there is no *in vivo* showing for the effectiveness of the peptides as claimed". It is respectfully submitted that Example 4 itself constitutes an *in vivo* showing for the effectiveness of the peptides as claimed. Also, contrary to an assertion by the Examiner, it is respectfully submitted that the Ueda *et al.* article supplied with the previous Amendment does show the *in vivo* effectiveness of a peptide, TNP-470, on the growth of carcinomas in an accepted animal model for testing drugs for efficacy in preventing or treating tumor growth and/or metastasis.

The Examiner argues that "Applicant's claims are directed to prevention, and there is no objective factual evidence in the specification or references enclosed or cited by Applicant to show that prevention has occurred since no adequate time was given to mimic the protocol administered in the animal models and allow evaluation of active immune response". Firstly, this line of reasoning seems to imply that Applicants have not ***proved*** in the specification that their invention functions in the manner that they say that it works in. While such considerations might be relevant to a rejection for failing to comply with the enablement requirement of the first paragraph of 35 U.S.C. §112, they are totally irrelevant to the present rejection (written description). Secondly, the present invention is thought to work through inhibition of angiogenesis, starving the tumor cells for nutrients and oxygen. The relevance of an immune response in the present invention is not apparent to Applicants' representative.

It is clear that the inventions of each of claims 22, 23, and 28 are fully described - in writing - in the specification. Withdrawal of the rejection of record is respectfully solicited.

Conclusion

If there are any remaining issues, the Examiner is invited to telephone Richard Gallagher (Reg. No. 28,781) at (703) 205-8008.

If necessary, the Commissioner is hereby authorized to debit Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §1.16 or §1.17, particularly extension of time fees.

Respectfully submitted,

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Enclosed: Ó Súilleabháin, *OncoLog*, June 2004, Vol. 49, No. 6.

From *OncoLog*, June 2004, Vol. 49, No. 6

Despite Initial Setbacks, Researchers Are Focusing on Antiangiogenic Therapy More Than Ever

by Kate Ó Súilleabháin

A few years ago, many people believed that the Holy Grail of cancer treatment had been found. Antiangiogenesis therapy was safe, elegant, and at first apparently effective. But the clinical results soon fell short of expectations. The tumors, it seemed, had found a way to circumvent even this most ingenious of treatment approaches. Despite the setbacks, however, angiogenesis remains a very tempting target, and researchers are exploring new agents and approaches to maximize the effects of antiangiogenic therapies.

A tempting target

Unlike a normal cell, a cancer cell is genetically unstable, causing it to replicate inaccurately. As a tumor grows, this genetic infidelity results in multiple subpopulations of cells with different biological characteristics. An antitumor treatment, be it chemotherapeutic drugs or radiation, will kill most of the billion or so cells in each cubic centimeter of tumor tissue. But invariably, some cells will be resistant to the treatment. After the treatment-sensitive cells are depleted, the resistant cells may rapidly divide to re-create a tumor that is inherently resistant to the therapy.

Given the heterogeneity of malignant cells within an individual tumor, not to mention among the various types of cancer, what common therapeutic target remains? The answer to this puzzle is surprisingly simple.

"We have searched for a uniform vulnerability among all tumor cells," said Isaiah J. Fidler, D.V.M., Ph.D., chair of the Department of Cancer Biology at The University of Texas M. D. Anderson Cancer Center. "And that vulnerability is, in fact, the nonnegotiable need for oxygen." Tumor cells cannot thrive unless supplied with oxygen and other nutrients that are transported by the blood. In fact, research in Dr. Fidler's laboratory revealed that tumor cells cannot survive at distances greater than 150 micrometers from a blood vessel.

These findings followed the discovery by Judah Folkman, M.D., and his colleagues at Children's Hospital Boston that pathologic angiogenesis, the process by which a malignant tumor develops new vessels, is the primary means by which cancer cells spread. Tumor cells migrate by using these vessels, which also supply the primary tumor with oxygen and other nutrients. The isolation of certain compounds that inhibit angiogenesis in mice fueled hopes of a cure for cancer. However, researchers soon found that angiogenesis can occur via any combination of multiple molecular signaling pathways, a characteristic termed "redundancy."

"We're dealing with a multifactorial process," said Roy S. Herbst, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology and codirector of the Clinical Trials Working Group. "There are now almost 20 known proangiogenic factors that are made by the tumor cells, stromal cells, or lymphocytes, which stimulate endothelial cell growth," he said. The division of endothelial cells, which line vessels, is blocked by antiangiogenic agents. But preventing these cells from multiplying may require targeting several molecules simultaneously—a daunting enterprise, considering the differences in expression and signaling among the various molecules governing angiogenesis in different cancers.

Far from being discouraged, however, researchers are focusing more than ever on agents that target the tumor vasculature. At least four major proteins and their receptors and signaling pathways commonly govern angiogenesis in solid tumors: platelet-derived growth factor, epidermal growth factor, vascular endothelial growth factor (VEGF), and fibroblast growth factor (basic and acidic). Therapies that either target these molecules or block their signaling pathways should be effective in preventing solid tumor growth and metastasis by preventing the formation of new vessels.

"Angiogenesis inhibition in the clinic is an even more challenging area than it was a few years ago," Dr. Herbst said. "We're trying to target angiogenesis using any number of different compounds." Dr. Herbst and his team are conducting a phase I/II trial of bevacizumab—a monoclonal antibody that targets VEGF and is the first antiangiogenesis agent to receive Food and Drug Administration approval—in combination with erlotinib in patients with non-small cell lung cancer. These data were presented at the 2004 Proceedings of the American Society of Clinical Oncology.

Other drugs targeting proteins important in angiogenesis are under study at M. D. Anderson. The Phase I Clinical Trials Working Group is exploring a number of investigational compounds in patients with advanced solid tumors.

Maintenance therapy

Dr. Herbst stresses a combinatorial approach involving angiogenesis inhibition along with other novel treatments, conventional chemotherapy, and/or radiotherapy. "Cancer is going to be treated as a chronic disease," he said. With the use of antiangiogenic agents as maintenance therapy, it is hoped that cancer can be controlled in the same way that medications are used to control hypertension and high cholesterol levels. "There are so many

different mutations in cancer that we'll certainly have to individualize the therapy from time to time based on a patient's particular tumor. Are we going to cure everyone with metastases? No, very few. But we hope to knock it down to its minimal bulk with chemotherapy and radiation therapy, which still have their important role. Perhaps these inhibitors can then be used as maintenance," said Dr. Herbst. Given that the side effects of antiangiogenesis agents have been minimal and that many are orally administered, prescribing them as maintenance therapy for outpatients is plausible.

But Dr. Fidler notes that targeting new vessels may not be enough. By the time most patients enter a clinical trial of an angiogenesis inhibitor (or any new treatment), their tumors are resistant to conventional therapy, are large, and have an established vasculature. "Inhibiting angiogenesis after it has already taken place is like closing the door on the barn after the horse has escaped," Dr. Fidler noted. Shrinking or destroying a tumor may require therapy that is not only antiangiogenic but also antivascular, targeting the existing vessels rather than endothelial cell turnover or new vessel growth.

"Seed and soil"

Clearly, the major challenge in treating cancer is not eradicating the primary tumor (which can be treated with radiation or surgery) but eradicating metastases, which are usually already present at the time of the initial diagnosis. The ability of a cell to metastasize is proportional to its genetic instability, making the cell populations of metastases even more heterogeneous than those of primary tumors—and hence more difficult to treat. Therefore, researchers are designing therapies that target not only metastases but also the sites of metastasis, an approach that hearkens back to Stephen Paget's "seed and soil" hypothesis of 1889. After observing that some cancers favored certain sites of metastasis over others, Paget maintained that metastasis can occur only if the cancer cell (the "seed") finds a favorable microenvironment at the site of metastasis (the "soil," or host). Researchers now understand that metastatic cells usurp homeostatic mechanisms that govern host physiologic processes because the host cells secrete growth factors that prompt tumor cell replication. Therefore, whereas traditional cancer therapies target the "seed," new approaches target the "soil," making the sites of metastasis inhospitable for cancer cells.

Preclinical models

The "seed and soil" hypothesis is guiding the development of mouse models to study different sites of metastasis in human lung cancer and other malignancies. Researchers at M. D. Anderson use a mouse model of lung cancer that closely resembles the disease in humans: a single tumor grows and expands within the lung and then spreads into the mediastinum and lymph nodes. In another mouse model designed to study brain metastasis of lung cancer, the same tumor cells are injected into the carotid artery, the main artery leading to the brain.

"We've also developed models of bone metastases, and we're now trying to develop models of different bones because lung cancer that spreads to the

femur can behave very differently from lung cancer that spreads to the spine," said Michael O'Reilly, M.D., an assistant professor in the Division of Radiation Oncology. "So we're now trying to identify any differences between different bone microenvironments." Supporting the "seed and soil" hypothesis, the data show that lung cancer growing in the brain behaves differently from lung cancer growing in the lung, as shown by unique patterns of production of proangiogenic molecules and different apoptotic indexes. Thus, angiogenesis inhibitors that are optimal in the primary organ may not be optimal in the metastatic site.

Dr. O'Reilly stated, "The ultimate goal is to translate the findings in these animals into the clinic and see if there are correlations [between animals and humans]. If we can figure straightforward ways to optimize antiangiogenesis therapies in the animals, we can optimize ways to kick off this therapy in patients."

For more information on this topic or for questions about M. D. Anderson's treatments, programs, or services, call the M. D. Anderson Information Line at (800) 392-1611 (in the United States) or (713) 792-3245 (in Houston and outside the United States).

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